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Cognitive Function as an Emerging Treatment Target for Marijuana Addiction

Mehmet Sofuoglu, M.D., **Dawn E. Sugarman, Ph.D.**, and **Kathleen M. Carroll, Ph.D.**
Yale University, School of Medicine, Department of Psychiatry and VA Connecticut Healthcare System, West Haven, CT

Abstract

Cannabis is the most widely used illicit substance in the world and demand for effective treatment is increasing. However, abstinence rates following behavioral therapies have been modest, and there are no effective pharmacotherapies for the treatment of cannabis addiction. We propose a novel research agenda and a potential treatment strategy, based on observations that both acute and chronic exposure to cannabis are associated with dose-related cognitive impairments, most consistently in attention, working memory, verbal learning, and memory functions. These impairments are not completely reversible upon cessation of marijuana use and moreover may interfere with the treatment of marijuana addiction. Therefore, targeting cognitive impairment associated with chronic marijuana use may be a promising novel strategy for the treatment of marijuana addiction. Preclinical studies suggest that medications enhancing the cholinergic transmission may attenuate cannabis-induced cognitive impairments, but these cognitive enhancing medications have not been examined in controlled human studies. Preliminary evidence from individuals addicted to other drugs suggests that computerized cognitive rehabilitation may also have utility to improve cognitive function in marijuana users. Future clinical studies optimally designed to measure cognitive function as well as drug use behavior would be needed to test the efficacy of these treatments for marijuana addiction.

Keywords

marijuana; cannabis; cognitive function; acetylcholine; cholinesterase inhibitors

1. Introduction

Marijuana (cannabis) is the most widely used illicit substance in the world. In the US, there are approximately 2 to 3 million new users of marijuana every year, and significantly, two thirds of them are between 12 and 17 years of age (Compton, Grant, Colliver, Glantz, & Stinson, 2004; ONDCP, 2008; SAMHSA, 2008). It is estimated that one out of 12 marijuana users will eventually become dependent on marijuana (Wagner & Anthony, 2002).

As with other addictions, cannabis-dependent individuals continue to use marijuana despite significant problems associated with its use. Marijuana use has been associated with low academic achievement, early school dropout, delinquency, legal problems, unemployment, cigarette smoking, and risk for the development of psychotic disorder (Ferdinand et al., 2005; Friedman, Glassman, & Terras, 2001; Hall & Degenhardt, 2009; Henquet et al., 2005). Although, there may be alternative explanations for these associations that need to be

✉Mehmet Sofuoglu, M.D., Yale University, Department of Psychiatry, VA Connecticut Healthcare System, 950 Campbell Ave., Bldg. 36/116A4, West Haven, CT 06516, Phone: (203) 937-4809, Fax: (203) 937-3472, mehmet.sofuoglu@yale.edu.

ruled out before a causal link can be established (Hall & Degenhardt, 2009; Sewell, Poling, & Sofuoglu, 2009). For example, the association between marijuana and nicotine addiction, could be due to common genetic vulnerability (Agrawal et al., 2008). However, reports from several countries (including the US, UK, and the Netherlands) indicate that the average age of initiation of marijuana use is decreasing, while the average delta-9-tetrahydrocannabinol (THC, the main psychoactive ingredient of cannabis) content of cannabis is increasing (ElSohly et al., 2000; Pijlman, Rigter, Hoek, Goldschmidt, & Niesink, 2005; Potter, Clark, & Brown, 2008). This may result in greater addictive potential as well as increased negative consequences of marijuana use.

While individuals seeking treatment for marijuana use problems was once comparatively rare (R.S. Stephens, Babor, Kadden, Miller, & MTP Research Group, 2002), increased treatment-seeking has been observed among marijuana users, making marijuana one of the most common illicit drugs of use among admissions to treatment programs in the US (SAMHSA, 2008). Currently, there are no effective medications for the treatment of marijuana addiction and available behavioral treatments are modestly effective (Nordstrom & Levin, 2007). Thus, development of effective treatment strategies, specifically for cannabis use disorders (dependence or abuse), is urgently needed.

Many studies have demonstrated that chronic exposure to marijuana is associated with dose-related cognitive impairments, most consistently in attention, working memory, verbal learning, and memory functions (Solowij & Battisti, 2008). Some studies also indicate that cognitive impairments in psychomotor speed, attention, memory and executive functions, are not fully reversible one month after cessation of marijuana use (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Medina et al., 2007). These findings could be due to long-lasting effects of marijuana or impairment of baseline cognitive functioning in marijuana users, compared to those who do not use marijuana. As reported recently, cognitive impairments in marijuana users may be predictive of poor treatment response (Aharonovich, Brooks, Nunes, & Hasin, 2008), raising the possibility that improving cognitive functioning may emerge as an important treatment strategy for marijuana use disorders. In this review, we articulate the rationale and a possible research agenda for greater focus on cognitive functioning as a treatment target for marijuana dependence. First we present an overview of the currently available treatments for marijuana addiction and review the neurocognitive effects of marijuana. We then outline potential treatments for neurocognitive impairment in marijuana users.

2. Current Treatments of Marijuana Addiction

Behavioral Treatments

The behavioral therapies that have been evaluated as treatments for marijuana addiction are those that have been demonstrated to be effective for other substance use disorders. These include contingency management (CM), motivational enhancement therapy (MET), cognitive-behavioral therapy (CBT), and combinations of those approaches. Early work by Roffman and Stephens evaluating motivational and cognitive approaches and brief treatments for cannabis abuse/dependence reported abstinence rates of approximately 15% at follow-up (R.S. Stephens, Roffman, & Curtin, 2000; R.S. Stephens, Roffman, & Simpson, 1994). Evaluations of very brief motivational approaches alone have produced mixed results in samples of young adult marijuana users (Martin & Copeland, 2008; McCambridge, Slym, & Strang, 2008; Walker et al., 2006). In particular, one study found that adolescents who participated in brief MET reduced their quantity and frequency of cannabis use, and reported less cannabis dependence symptoms at 3-month follow-up (Martin & Copeland, 2008). However, two other studies with adolescents found that although participants reduced their cannabis use over time, there were no significant differences in reductions between MET

and a drug information and advice condition (McCambridge et al., 2008), or a delayed feedback control condition (Walker et al., 2006).

The Marijuana Treatment Project, a large multisite trial of behavioral treatments, compared the effectiveness of delayed treatment, compared to 2 sessions of brief treatment or 9 sessions of extended treatment. The results indicated significantly better outcomes for the extended treatment compared to the brief treatment and for both active treatments over the delayed treatment control (MTP Research Group, 2004). However, abstinence rates, which were as high as 23% for the extended treatment condition at the end of treatment, fell to 15% at follow-up.

Several studies have evaluated the efficacy of contingency management approaches, which provide tangible reinforcers contingent on submission of marijuana-free urine specimens, alone and in combination with other therapies (A.J. Budney, Higgins, Radonovich, & Novy, 2000; A. J. Budney, Moore, Rocha, & Higgins, 2006; Carroll et al., 2006; Kadden, Litt, Kabela-Cormier, & Petry, 2007). In general, while approaches which include CM are associated with higher rates of within-treatment abstinence from marijuana, the effects of CM tend to fall off more rapidly after treatment ends compared with those which include CBT. A recent cost analysis suggested CBT may prove a more cost-effective approach for cannabis dependence given its relative durability (Olmstead, Sindelar, Easton, & Carroll, 2007).

Thus, while the small but growing literature on behavioral treatments for cannabis use disorders suggests that significant effects over control or comparison conditions have been found with some consistency for contingency management and CBT, effect sizes and abstinence rates at follow-up remain modest (Denis, Lavie, Fatseas, & Auriacombe, 2006). One year abstinence rates ranging from 9 to 28 percent (A. J. Budney, Roffman, Stephens, & Walker, 2007; Denis et al., 2006; Kadden et al., 2007) indicate that there is room for improvement. Brief MET has shown some promise in reducing marijuana use over time (Martin & Copeland, 2008), but these findings are not consistent in the literature (McCambridge et al., 2008; Walker et al., 2006). Thus, it may be beneficial to investigate ways to enhance these treatments. In addition, effective pharmacological treatments for marijuana addiction should be explored.

Pharmacotherapies

Cannabis effects are mediated by two types of cannabinoid receptor, designated CB1 and CB2 (Brown, 2007; Howlett et al., 2002). The CB1 receptors are densely distributed in the hippocampus, prefrontal cortex, anterior cingulate, basal ganglia, and cerebellum (Herkenham et al., 1990). CB1 receptors are predominantly located in the presynaptic terminals and modulate the release of other neurotransmitters including GABA, glutamate, norepinephrine, and acetylcholine (ACh) (Heifets & Castillo, 2009). CB2 receptors are found mostly within the immune cells. The endogenous cannabinoids (endocannabinoid), anandamide (AEA) and 2-arachidonyl glycerol (2-AG) also target these receptors and have a wide range of functions including modulation of pain, motor activity, motivation, reward, stress response, and cognitive processes (Heifets & Castillo, 2009).

Several potential medications have been identified for the pharmacological treatment of marijuana addiction, with some promising initial findings (Hart, 2005). The cannabis antagonist, rimonabant, appears to attenuate the subjective and physiological effects of smoked marijuana (Huestis et al., 2001). Unfortunately, rimonabant has been withdrawn from the market due to adverse events including depression and suicidality (Le Foll, Gorelick, & Goldberg, 2009). There are several other cannabinoid antagonists that are in development (Janero & Makriyannis, 2009). For example, cannabidiol, a major ingredient of

cannabis, blocks THC-induced acute psychotic symptoms and anxiety in humans (Bhattacharyya et al., 2009; Zuardi, 2008). The oral cannabinoid agonist, THC, has been shown to attenuate marijuana withdrawal symptoms in both outpatient and controlled human laboratory studies (A. J. Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007). The combination of lofexidine and oral THC showed promising results in alleviating withdrawal and preventing relapse in a human laboratory model (Haney et al., 2008). Lofexidine inhibits noradrenergic activity by stimulating α_2-adrenergic receptors (Louis, Jarrott, & Conway, 1988). Nevertheless, to date, no pharmacological agent has demonstrated efficacy in randomized clinical trials (Nordstrom & Levin, 2007).

3. Neurocognitive Effects of Marijuana

In rodents and non-human primates, THC and synthetic cannabinoids impair learning and memory processes assessed with a range of tasks including, the eight-arm radial-maze (Han & Robinson, 2001; Mallet & Beninger, 1998; Nava, Carta, Battasi, & Gessa, 2000; Winsauer, Lambert, & Moerschbaecher, 1999; Zimmerberg, Glick, & Jarvik, 1971), two-component instrumental discrimination task (Han & Robinson, 2001; Mallet & Beninger, 1998; Nava et al., 2000; Winsauer et al., 1999; Zimmerberg et al., 1971), time interval estimation task based on a fixed-interval schedule (Han & Robinson, 2001; Mallet & Beninger, 1998; Nava et al., 2000; Winsauer et al., 1999; Zimmerberg et al., 1971), conditional discriminations (Han & Robinson, 2001; Mallet & Beninger, 1998; Nava et al., 2000; Winsauer et al., 1999; Zimmerberg et al., 1971), and two-task procedure tasks (Han & Robinson, 2001; Mallet & Beninger, 1998; Nava et al., 2000; Winsauer et al., 1999; Zimmerberg et al., 1971). Consistent with preclinical studies, marijuana or THC administration in humans have been reported to produce acute, transient, dose-related impairments in learning, short-term memory, working memory, time-estimation, inhibitory control, decision making, and attention (Hart, van Gorp, Haney, Foltin, & Fischman, 2001; Heishman, Huestis, Henningfield, & Cone, 1990; Hooker & Jones, 1987; Leweke et al., 1998; Marks & MacAvoy, 1989; McDonald, Schleifer, Richards, & de Wit, 2003; Miller, McFarland, Cornett, & Brightwell, 1977; Ramaekers et al., 2006). In these studies, verbal learning and memory, working memory, and sustained attention functions were most consistently impaired following acute cannabis administration (Solowij & Battisti, 2008).

Chronic heavy marijuana use is alsoassociated with impairments in verbal learning and memory, sustained attention, and executive functioning (Bolla et al., 2002; Pope, Gruber, & Yurgelun-Todd, 1995; Pope & Yurgelun-Todd, 1996; Solowij, 1995; Solowij, Michie, & Fox, 1995; Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti et al., 2002). In a recent study, after 20 days of abstinence, adolescent marijuana users, compared to controls, showed deficits in psychomotor speed, attention, memory and executive functioning (Medina et al., 2007). Number of lifetime marijuana use episodes was associated with greater cognitive deficits, suggesting a cumulative dose effect of marijuana use (Medina et al., 2007). Further, following a 28-day abstinence, heavy marijuana users performed more poorly than lighter userson a verbal learning and memory task (Bolla et al., 2002), while others reported recovery of cognitive function after 28 days of abstinence (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001). The persistence of cognitive impairments, for at least weeks following abstinence from marijuana use, supports the need to address cognitive impairments early in treatment.

In contrast to these studies, other studies reported minimal (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003) or no lasting effects of chronic cannabis use on overall IQ, attention, working memory, and abstract reasoning (Fried, Watkinson, & Gray, 2005; Jager, Kahn, Van Den Brink, Van Ree, & Ramsey, 2006). Important to note that, cannabis-induced cognitive impairments may be dependent on the age of onset of cannabis use; in particular,

those starting before the age of 17 having greater impairment (Kempel, Lampe, Parnefjord, Hennig, & Kunert, 2003; Pope et al., 2003). Thus, age of onset and other baseline variables, like IQ (Bolla et al., 2002), may explain the conflicting findings regarding long-term marijuana use on cognitive outcomes.

Chronic cannabis exposure is associated with varying degrees of tolerance depending on the outcome measures (Lichtman & Martin, 2005). In a previous study, subjective high and sedation were lower in frequent marijuana users, compared to occasional users, in response to a single oral dose of 15 mg THC (Kirk & de Wit, 1999). In contrast, there were no differences between groups for performance on the digit symbol substitution test, suggesting lack of tolerance to cannabis-induced cognitive impairment (Kirk & de Wit, 1999). Two recent studies compared occasional and frequent marijuana users for the acute THC-induced cognitive impairment (D'Souza et al., 2008; Ramaekers, Kauert, Theunissen, Toennes, & Moeller, 2009). Frequent users had attenuated impairment to divided attention, verbal learning and memory tasks but not to vigilance (D'Souza et al., 2008), or motor inhibition tasks (Ramaekers et al., 2009) suggesting differential tolerance for the THC responses. These findings are consistent with preclinical studies demonstrating that chronic treatment with cannabinoid agonist lead to differential molecular, cellular, and behavioral changes that are dependent on the brain region and the outcome measures (Lichtman & Martin, 2005; McKinney et al., 2008).

The potential neural substrates of these deficits have been examined in both preclinical and human functional imaging studies. The hippocampus, a region that is long associated with learning and memory, has been closely examined for cannabis-induced cognitive impairment. The hippocampus shows a high density of CB1 receptors, as well as endogenous cannabinoid anandamide (Mackie, 2005). In rats, injection of cannabinoid agonist CP-55,940 systemically or into the hippocampus similarly disrupted working memory performance (Lichtman, Dimen, & Martin, 1995). Further, cannabinoid agonists inhibit hippocampal long-term potentiation (LTP), the putative neural substrates of learning and memory (Collins, Pertwee, & Davies, 1995; Davies, Pertwee, & Riedel, 2002; Hoffman, Oz, Yang, Lichtman, & Lupica, 2007; Misner & Sullivan, 1999; Terranova, Michaud, Le Fur, & Soubrie, 1995). Mice strains lacking CB1 receptors have been reported to show enhanced LTP (Bohme, Laville, Ledent, Parmentier, & Imperato, 2000) and an enhanced memory function (Reibaud et al., 1999). These findings further support the role of CB1 receptors in learning and memory functions. Consistent with these preclinical findings, long-term heavy marijuana users had reduced hippocampus and amygdala volumes, and the size of the left hippocampus was correlated to the severity of marijuana use (Yucel et al., 2008). These data suggest that hippocampus plays a critical role in cannabis-induced disruption in learning and memory, although other brain regions, especially the prefrontal cortex, also contribute to cognitive impairment induced by cannabis (Egerton, Allison, Brett, & Pratt, 2006). For example, marijuana abusers were shown to have lowerregional cerebral blood flow (rCBF) during a resting condition in the ventral prefrontalcortex even after 26-hours of abstinence (Block et al., 2000). Similarly, long-term marijuana users had hypoactivity in the anterior cingulate cortex and the left lateral prefrontal cortex (LPFC) during the Stroop test performance (Eldreth, Matochik, Cadet, & Bolla, 2004; Gruber & Yurgelun-Todd, 2005).

4. Neurobiological Mediators of the Cognitive Impairment by Marijuana

The exact neurobiological mechanisms underlying the marijuana-induced cognitive impairment remain to be elucidated (Egerton et al., 2006). Accumulating evidence from preclinical studies suggests that the cholinergic system may have an important role in the cognitive impairment induced by marijuana (Carta, Nava, & Gessa, 1998; Gessa, Casu, Carta, & Mascia, 1998; Gessa, Mascia, Casu, & Carta, 1997; Mishima, Egashira,

Matsumoto, Iwasaki, & Fujiwara, 2002; Nava et al., 2000; Nava, Carta, Colombo, & Gessa, 2001). Acetylcholine (ACh) is the neurotransmitter for the cholinergic system. ACh participates in many CNS functions including attention, working memory, motivation, and reward (Briand, Gritton, Howe, Young, & Sarter, 2007; Smythies, 2005). These diverse cholinergic effects are mediated by nicotinic and muscarinic type ACh receptors. Cholinergic neurons are either projection neurons, terminating diffusely in the brain including in the hippocampus, prefrontal cortex, or interneurons, which are located mainly in the striatum and nucleus accumbens (Mesulam, 2004). While cholinergic projection neurons are critical in cognitive function, cholinergic interneurons integrate the cortical and subcortical information related to motivation and reward (Berlanga et al., 2003). ACh is implicated in pathophysiology of Alzheimer's disease, schizophrenia, and other disorders associated with declined cognitive function (Smythies, 2005; M. Sofuoglu & Mooney, 2009).

Cannabinoid agonist THC inhibit cholinergic transmission in the brain and performance deficits induced by cannabis on the working maze task resemble those observed with the cholinergic antagonist scopolamine (Varvel, Hamm, Martin, & Lichtman, 2001). Consistent with these findings, CB1 receptors located on the cholinergic terminals have been shown to control ACh release (Degroot et al., 2006). In many preclinical studies, administration of THC or cannabinoid agonists tetrahydrocannabinol or WIN 55,212-2 reduced ACh release in the hippocampus in freely moving rats or in hippocampal slices (Carta et al., 1998; Gessa et al., 1998; Gessa et al., 1997; Mishima et al., 2002; Nava et al., 2000; Nava et al., 2001). The reduction in cannabis-induced ACh release in hippocampus was significantly correlated with the impairment of working memory (Gessa et al., 1998). Further, tolerance did not develop to the THC-induced reduction in ACh release in hippocampus (Gessa et al., 1998). These findings are consistent with the studies showing lack of tolerance to some marijuana-induced cognitive impairments (Kirk & de Wit, 1999). This cannabinoid effect on ACh release seems to be less in the medial-prefrontal cortex and is not observed in the striatum (Gessa et al., 1998).

Of particular clinical interest, the cholinesterase inhibitors physostigmine or tetrahydroaminoacridine, dose-dependently reversed the THC –induced reduction in correct choices and increase in errors in the 8-arm radial maze task in rats (Mishima et al., 2002). Further, tetrahydroaminoacridine at 1 mg/kg, which improved the impairment of spatial memory, also reversed the THC-induced release of Ach in dorsal hippocampus (Mishima et al., 2002). Similar findings were observed using another cholinesterase inhibitor, eptastigmine, in rats. In that study, CP 55,940 dose-dependently impaired working-memory function deficits including errors, correct choices, and average time. Pretreatment with eptastigmine, significantly reversed the CP 55,940-induced impairment for mean total number of errors and mean number of correct choices (Braida & Sala, 2000). These effects seem to be mediated by the M1 and M3 type muscarinic cholinergic receptors (Fukudome et al., 2004; Ohno-Shosaku et al., 2003). There is also a functional interaction between the nicotinic and cannabis receptors. In preclinical studies, nicotine enhanced the cannabis-induced hypothermia, antinociception, anxiolytic-like response, and conditioned place preference but attenuated cannabis tolerance (Valjent, Mitchell, Besson, Caboche, & Maldonado, 2002). Nicotine also facilitated cannabis discrimination in rats (Solinas et al., 2007) but another study failed to replicate these findings in mice (Vann et al., 2009). Consistent with these findings, a 21-mg nicotine patch, compared to placebo, enhanced several responses to marijuana cigarettes including the heart rate and the subjective rating of "stimulated" on the Addiction Research Center Inventory (ARCI) in humans (Penetar et al., 2005). In adolescent tobacco smokers with or without cannabis use history, Jacobson et al. (Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007) reported that nicotine intake by cigarette smoking may alleviate cannabis-related verbal memory and learning impairment.

These preliminary findings suggest that nicotine may attenuate cannabis-induced verbal memory deficits.

5. Neurocognitive Impairment and Treatment of Marijuana Addiction

Although the acute and chronic effects of marijuana on cognitive function have been well documented, the impact of cognitive function on treatment outcomes has not been well-studied (Bolla et al., 2002; Hart et al., 2001; Heishman et al., 1990; Hooker & Jones, 1987; Leweke et al., 1998; Marks & MacAvoy, 1989; McDonald et al., 2003; Miller et al., 1977; Pope et al., 1995; Pope & Yurgelun-Todd, 1996; Ramaekers et al., 2006; Solowij, 1995; Solowij et al., 1995; Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, & Vendetti, 2002). In a recent study, Aharonovich and colleagues evaluated 20 marijuana dependent patients enrolled in a randomized treatment study, which included cognitive behavioral therapy (CBT) and motivational enhancement therapy (MET). Cognitive impairments in abstract reasoning, spatial and processing accuracy were predictive of poor treatment retention (Aharonovich et al., 2008). While limited by a very small sample size, these findings are consistent with previous reports of negative effects of cognitive impairments on treatment retention among cocaine and poly-drug users (Aharonovich et al., 2006; Aharonovich, Nunes, & Hasin, 2003; Bates, Pawlak, Tonigan, & Buckman, 2006; Donovan, Kivlahan, & Walker, 1984; O'Leary, Donovan, Chaney, & Walker, 1979). In a study with poly-drug users, participants who scored low (<7) on the Block Design and Digit Symbol subtest of the WAIS-R (Wechsler Adult Intelligence Scale-Revised) remained in treatment a significantly shorter amount of time (Fals-Stewart, 1993; Fals-Stewart & Schafer, 1992). In a follow-up study, poly-drug users in a residential treatment program who obtained a neuropsychological test battery summary score of $T < 40$, had shorter lengths of stay in treatment and were viewed less favorably by treatment staff (Fals-Stewart, 1993). Moreover, in recent research, poly-drug users with lower estimated WAIS-R IQ scores were less engaged in treatment than participants with higher estimated IQ scores (Katz et al., 2005). Research with cocaine users found similar results; such that participants with low cognitive scores were more likely to drop out of treatment (Aharonovich et al., 2006; Aharonovich et al., 2003). In particular, dropouts had significantly poorer scores on tests of cognitive speed, accuracy, and attention (Aharonovich et al., 2006). The results of these studies suggest that cognitive functioning significantly affects substance users' ability to engage and remain in treatment. Although there is a dearth of research is this area with marijuana users, the literature with poly-drug and cocaine users highlights the potential of greater focus on the clinical and prognostic significance of the cognitive impairments in treatment-seeking marijuana users.

6. Treatment Approaches Targeting Neurocognitive Impairment in Marijuana Users

6A. Behavioral Approaches

Among behavioral approaches, computerized cognitive rehabilitation has demonstrated some promise among schizophrenics as well as in drug users in residential settings (Bell, Bryson, Greig, Corcoran, & Wexler, 2001; Fals-Stewart, 1994). Computerized neurocognitive rehabilitation interventions are designed to enhance cognitive skills though exercises that target problem-solving skills, attention, memory, and abstract reasoning (Fals-Stewart & Lam, in press). The PSYCogReHab program has been used in several studies (Fals-Stewart & Lam, in press; Fals-Stewart & Lucente, 1994; Grohman, Fals-Stewart, & Donnelly, 2006) and consists of four modules (Foundations, Visuospatial, Problem Solving, and Memory) that aim to enhance function in several domains, including: executive functioning, memory, planning, organization technology, decision making, judgment,

sequencing/systems thinking, attention training, visual attention, focusing, concentration, auditory attention, and sensory integration. The modules adapt to the individual's performance, and mastery of a task must be achieved before the individual can move on to the next task. Research in the area of cognitive rehabilitation shows that cognitively-impaired poly-drug abusers who receive computer-assisted cognitive rehabilitation improved in cognitive performance tests, were rated as more engaged in treatment, and remained in treatment longer compared to control participants (Fals-Stewart & Lucente, 1994; Grohman et al., 2006). Recent research replicated these findings, providing strong evidence that cognitive improvement can be accelerated, which in turn can lead to better treatment outcomes (Fals-Stewart & Lam, in press). Computerized cognitive rehabilitation approaches have not yet been evaluated among marijuana users.

6B. Pharmacological Approaches

There are several cognitive-enhancers that may potentially be used for the treatment of cannabis addiction (M. R. Farlow, 2009; Monti & Contestabile, 2009; Tarditi, Caricasole, & Terstappen, 2009). In this review, we will focus on the cholinesterase inhibitors since preclinical studies suggest that increasing synaptic ACh levels with cholinesterase inhibitors may alleviate cannabis-induced spatial and working memory deficits (Mishima et al., 2002). Several cholinesterase inhibitors, including tacrine, rivastigmine, donepezil, and galantamine are available for clinical use for the treatment of dementia (Birks, 2006; M. Farlow, 2002; Giacobini, 2004). These medications have also been evaluated for other disorders characterized with cognitive impairment, including Parkinson's disease, traumatic brain injury, and schizophrenia (Camicioli & Gauthier, 2007; Khateb, Ammann, Annoni, & Diserens, 2005; Ochoa & Clark, 2006). The pharmacological as well as side effect profiles of the various cholinesterase inhibitors differ among each other. Cholinesterase inhibitors have a good safety profile and their potential use in cannabis addicted individuals is feasible. The most common side effects of cholinesterase inhibitors include diarrhea, nausea, vomiting, loss of appetite, and dizziness (Birks, 2006; Hansen et al., 2008; Ritchie, Ames, Clayton, & Lai, 2004). Tacrine has limited use due to hepatotoxicity and short half-life. Previous studies have shown that while a wide-range of cognitive functions including learning, memory and visuospatial abilities seem to be improved with cholinesterase inhibitors, these medications may be particularly effective in improving attentional function (Galvin et al., 2008; Lucas-Meunier, Fossier, Baux, & Amar, 2003). Attention, which refers to the individual's ability to selectively concentrate on one aspect of the environment while ignoring potential distracters, underlies or contributes to many other cognitive functions (Knudsen, 2007). As recently reviewed by De Wit (de Wit, 2009), a relationship between attentional processes and drug addiction has started to emerge more clearly. Lapses in attention have been proposed as an important antecedent of the drug-seeking response in addicted individuals (Acheson & de Wit, 2008; de Wit, 2009). In a recent study with abstinent cocaine users, we have shown that galantamine treatment, improved sustained attention function (M. Sofuoglu, Poling, Sewell, Waters, & Carroll, 2009) assessed with the Rapid Visual Information Task. Systematic human studies examining the cholinergic system in cannabis-induced cognitive impairment have not yet been undertaken.

7. Summary: Cognitive impairment as a treatment target for marijuana addiction

In this review, we have summarized available evidence demonstrating that marijuana users show impaired cognitive functioning, especially in working memory and verbal learning/memory functions. Moreover, there is preliminary evidence that impaired cognitive functioning predicts poor treatment response in marijuana users. Preclinical studies suggest that cholinesterase inhibitors may alleviate the cognitive impairments induced by cannabis

but they have not yet been examined for the treatment of marijuana addiction in humans. Studies conducted in individuals addicted to other drugs suggest that cognitive rehabilitation may be an effective strategy to improve cognitive function and treatment outcomes in drug users. Work in this area is nascent, however, and multiple basic questions have not been addressed, including:

1) Will cognitive improvement lead to better treatment outcomes in marijuana users?

As summarized above, cognitive deficits in marijuana users including working memory, response inhibition, and verbal learning functions have been well-documented. There is some evidence that cognitive deficits in marijuana users may be associated with poorer retention in treatment. However, it is not clear whether improvement in cognitive functions will lead to better retention or better treatment outcomes for marijuana addiction.

2) What is the potential therapeutic role of cognitive enhancing medications in marijuana users?

Most behavioral treatments for addictions are predicated on the ability of the patient to attend to treatment, understand interventions and behavioral change strategies, and be able to implement them (Ersche & Sahakian, 2007; Fals-Stewart & Bates, 2003; Fals-Stewart, Schafer, Lucente, Rustine, & Brown, 1994). Intact cognitive functioning may be particularly crucial for more complex approaches such as CBT that emphasize cognitive re-training and learning of new behavioral skills. Moreover, inhibitory function and ability to maintain awareness of long term goals are key elements of good treatment outcomes irrespective of treatment type. Thus, medications like cholinergic enhancers may be effective for the pharmacotherapy of addiction by reducing drug use through enhancing inhibitory control. Alternatively, cholinergic enhancers can be used to augment response to behavioral treatments for marijuana addiction. There are several examples of augmentation of behavioral treatment with cognitive enhancer cycloserine for the treatment of phobias and other anxiety disorders (McNally, 2007; Ressler et al., 2004; Santa Ana et al., 2009; Wilhelm et al., 2008). Such augmentation strategies remain to be evaluated for the treatment of marijuana addiction.

3) What specific cognitive functions are most strongly related to improved treatment outcome?

The cognitive antecedents of addictive behaviors are the focus of intense research (de Wit, 2009; M. Sofuoglu, 2010; Vocci, 2008). Among cognitive functions, reduced inhibitory control, also commonly called impulsivity, has been the centerpiece for the continuation of drug use behavior (Everitt et al., 2007; Kalivas & Volkow, 2005; Porrino, Smith, Nader, & Beveridge, 2007). However, inhibitory function is a complex construct with multiple dimensions including response inhibition and faulty decision making (or insensitivity to consequences) (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002; Li et al., 2008; Li, Milivojevic, Kemp, Hong, & Sinha, 2006). More recently, attention and working memory have also been recognized as separate dimensions of inhibitory control (Chambers, Garavan, & Bellgrove, 2009; Hester & Garavan, 2004; Posner & Rothbart, 2007). The importance of these cognitive functions in predicting treatment outcomes in addicted populations remain to be determined.

To summarize, the evaluation of pharmacological or behavioral interventions targeting cognitive functioning in marijuana users suggests several potential areas for future research. In particular, the cognitive functions that are most predictive of treatment outcomes among marijuana users are not yet well studied in clinical trials. Selecting validated cognitive tests with good psychometric properties and that are sensitive to pharmacological or behavioral interventions will be a crucial step, as will exploration of the extent to which improvements

in cognitive functioning can be evaluated through functional imaging techniques (Hester & Garavan, 2004; Jacobsen et al., 2007; Yucel et al., 2008). Finally, optimal timing of initiating treatments is a key issue, particularly regarding whether treatments will be more effective if introduced after an initial period of abstinence or whether they can be used to facilitate abstinence if started while the individual is still using marijuana. Clinical studies optimally designed to measure cognitive function as well as drug use behavior, would be needed to address these questions.

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